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— of inventorship (Rule 4.17(iv))

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(54) Title: TREATMENT OF IMMUNE DISEASE BY MUCOSAL DELIVERY OF ANTIGENS USING GENETICALLY MOD-  
IFIED LACTOBACILLUS

(57) Abstract: The present invention relates to the treatment of autoimmune and allergic diseases by mucosal delivery by micro-  
organism, in particular *Lactococcus lactis*, of secreted immunodominant antigens.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2008/050900

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K39/35  
ADD. C12R1/225

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61K C12R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, Sequence Search

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRUISSELBRINK A ET AL: "RECOMBINANT LACTOBACILLUS PLANTARUM INHIBITS OUSE DUST MITE-SPECIFIC T-CELL RESPONSES" CLINICAL AND EXPERIMENTAL IMMUNOLOGY, OXFORD, GB, vol. 126, no. 1, 1 October 2001 (2001-10-01), pages 2-08, XP001078798 ISSN: 0009-9104	1-9, 12-27, 30-44
Y	the whole document	11,29

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

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Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/050900

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WIEDERMANN URSULA: "Prophylaxis and therapy of allergy by mucosal tolerance induction with recombinant allergens or allergen constructs"</p> <p>CURRENT DRUG TARGETS. INFLAMMATION AND ALLERGY, BENTHAM SCIENCE PUBLISHERS, HILVERSUM, NL, vol. 4, no. 5, 1 October 2005 (2005-10-01), pages 577-583, XP009091104</p> <p>ISSN: 1568-010X</p> <p>page 582</p>	1-9, 12-27, 30-44
X	<p>HUIBREGTSE INGE L ET AL: "Mucosal delivery of ovalbumin by the genetically modified L. lactis suppresses systemic and local inflammatory T-cell responses in D011.10 mice"</p> <p>GASTROENTEROLOGY, vol. 130, no. 4, Suppl. 2, April 2006 (2006-04), page A557, XP009101996</p> <p>&amp; DIGESTIVE DISEASE WEEK MEETING/107TH ANNUAL MEETING OF THE AMERICAN-GASTROENTEROLOGICAL-ASSOCIATION; LOS ANGELES, CA, USA; MAY 19 24, 2006</p> <p>ISSN: 0016-5085</p> <p>abstract</p>	1-9, 12-27, 30-44
X	<p>WO 97/14806 A (UNIV CAMBRIDGE TECH [GB]; STEIDLER LOTHAR [BE]; REMAUT ERIK [BE]; WELL) 24 April 1997 (1997-04-24)</p> <p>claims 8,31</p>	1-9, 12-27, 30-44
X	<p>MAASSEN C B M ET AL: "Reduced experimental autoimmune encephalomyelitis after intranasal and oral administration of recombinant lactobacilli expressing myelin antigens"</p> <p>VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, vol. 21, no. 32, 1 December 2003 (2003-12-01), pages 4685-4693, XP004469685</p> <p>ISSN: 0264-410X</p> <p>the whole document</p>	1-9, 12-27, 30-44

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/050900

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HUIBREGTSE ET AL: "Induction of Antigen-specific Oral Tolerance by Genetically Modified Lactococcus Lactis Delivering DQ8-specific Immunodominant Gliadin Epitopes to Gluten-sensitized Class II Transgenic Mice" CLINICAL IMMUNOLOGY, ACADEMIC PRESS, US, vol. 123, 1 January 2007 (2007-01-01), pages S53-S54, XP022076968 ISSN: 1521-6616 abstract	1-9, 12-27; 30-44
Y	WO 03/096979 A (UNIV LELAND STANFORD JUNIOR [US]; KHOSLA CHAITAN [US]; HAUSCH FELIX [C] 27 November 2003 (2003-11-27) page 8 discloses 100% identical polypeptide compared to SEQ ID NO: 6 page 2 page 8	11,29
Y	WO 2004/045392 A (UNIV LELAND STANFORD JUNIOR [US]; KHOSLA CHAITAN [US]; SHAN LU [US]) 3 June 2004 (2004-06-03) page 5 discloses 100% identical polypeptide compared to SEQ ID NO: 8 page 1 page 5	11,29
A	STEIDLER LOTHAR ET AL: "Therapeutic drug delivery by genetically modified Lactococcus lactis" ANNALS OF THE NEW YORK ACADEMY OF SCIENCES BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXEN, UK SERIES : ANNALS OF THE NEW YORK ACADEMY OF SCIENCES (ISSN 0077-8923(PRINT)), 2006, pages 176-186, XP009101905 & INTERNATIONAL SYMPOSIUM ON INFLAMMATORY BOWEL DISEASES; MUNSTER, GERMANY; SEPTEMBER 01 -03, 2005 ISSN: 1-57331-568-0(H) cited in the application page 179	
A	NORTON P M ET AL: "PROGRESS IN THE DEVELOPMENT OF LACTOCOCCUS LACTIS AS A RECOMBINANT MUCOSAL VACCINE DELIVERY SYSTEM" FOLIA MICROBIOLOGICA, PRAQUE, CZ, vol. 40, no. 3, 1 January 1995 (1995-01-01), pages 225-230, XP000645430 ISSN: 0015-5632 the whole document	

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# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2008/050900

C(Continuation), DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MAYER LLOYD ET AL: "Therapeutic potential of oral tolerance" NATURE REVIEWS IMMUNOLOGY, vol. 4, no. 6, June 2004 (2004-06), pages 407-419, XP009101988 ISSN: 1474-1733 the whole document	
P, X	WO 2007/063075 A (ACTOGENIX NV [BE]; ROTTIERS PIETER [BE]; SNOECK VEERLE [BE]) 7 June 2007 (2007-06-07) page 3 - page 4 claim 70 page 37 - page 39	1-9, 12-27, 30-44

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2008/050900

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:  
1-9,12-27,30-44 (completely), 10,11,28,29 (partially)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; It is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9,12-27,30-44 (all completely),10,28 (all partially)

A microorganism expressing gliadin antigen and compositions/methods to induce antigen-specific tolerance  
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2. claims: 10,28 (all partially)

A microorganism or method using said microorganism wherein hordein is expressed as antigen.  
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3. claims: 11,29 (all partially)

see invention 2 with relation to SEQ ID NOs: 2 and 4 (HLA-DQ8)  
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4. claims: 11,29 (all partially)

see invention 2 with relation to SEQ ID NOs: 6 and 8 (HLA-DQ2)  
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/050900

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9714806	A	24-04-1997	AU 7315496 A	07-05-1997
			BR 9610929 A	21-12-1999
			CN 1202934 A	23-12-1998
			EP 0871748 A2	21-10-1998
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			NO 981746 A	22-06-1998
			NZ 320418 A	27-03-2000
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			EP 1507549 A2	23-02-2005
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			CA 2502700 A1	03-06-2004
			EP 1563300 A2	17-08-2005
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			CA 2631598 A1	07-06-2007
			EP 1957100 A1	20-08-2008